Open label extension studies: research or marketing?

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Open label extension studies allow continued prescribing of unlicensed drugs after a randomised trial, but it is unclear whether patients or drug companies are benefiting the most

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Properly designed and conducted open label extension studies can provide rigorous information on long term safety and tolerability of potential new drugs. This in turn can benefit the licensing application for the drug by providing longer term data that would otherwise not be available until after the licence was approved. Nevertheless, the conduct of such studies raises several ethical and scientific concerns.[1 2] As with any research method, there are good and bad examples. However, open label extension studies seem particularly prone to the pressures of marketing over good research methods and research ethics. We revisit some of these issues and argue that we need to change our approach to the ethical review of such studies.

Open label extension studies

Open label extension studies typically follow a double blind randomised placebo controlled trial of a new drug. At the end of the double blind phase, participants are invited to enrol in an extension study. The study will normally be longer than the randomised trial (two years is not uncommon but they often continue until the drug is licensed). All participants in the extension study are given the study drug, and both they and the investigators know this. The objective is primarily to gather information about safety and tolerability of the new drug in long term, day to day use.

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Participants in open label extension studies need more information

Use of open label studies after phase III trials is relatively common. In 2004, the multicentre research ethics committee for Wales reviewed three open label extension studies compared with 19 phase III studies of new drugs, a ratio of just over 6:1. However, a recent Medline search for studies between 2000 and 2004, produced only 86 open label studies but over 2000 phase III studies, a ratio of 23:1. This suggests that many open label studies are never published.

Issues of consent

The way that open label extension studies recruit raises several questions about informed consent. Participants are invited to join the extension study as soon as their involvement in the randomised controlled phase III study is finished. They do not know whether they have been taking active or placebo treatment, and investigators will not normally unblind the study at this point. Participants will thus base their decision on their previous study experience. Given that participants in either arm of the trial may have had positive or negative outcomes, their experience during the trial and their perception of the efficacy of the treatment they have received cannot be a sound basis on which to make such a judgment. In addition, as the results of the phase III study are unavailable, participants will be receiving a drug without the evidence that the treatment is any better than the standard treatment; it may potentially be worse.

The clinical picture of some participants may also have changed during the phase III trial. Participants may no longer meet the inclusion criteria or may no longer require treatment. At the conclusion of a trial participants are normally reviewed by their doctor. Enrolment in an extension study could result in

participants taking a drug that was not clinically justified (and often for a long time).

Another problem is that participants in the phase III trial are often told of the possibility of the extension study at the time of recruitment. This raises a separate ethical concern about the validity of consent to the phase III trial. If patients who think their present treatment options are unsatisfactory are told that enrolment in a short randomised controlled trial will ensure the possibility of open label treatment with a new drug in the near future, this may induce them to consent to the initial study and might amount to coercion.

Further pressure may come from researchers trying to get a high recruitment rate. Researchers conducting an open label extension study can only recruit from the participants in the phase III study. They may therefore feel under pressure to recruit to ensure the scientific merit of the study and continued income from the funder. This may in turn encourage investigators to place pressure on participants to take part. Unless all of these possibilities are made clear to a potential participant during recruitment and the researcher is not under undue pressure, the validity of the participants' consent is in question.

Scientific merit

The validity of data from open label extension studies raises further questions. Open label extension studies are commonly used to assess long term tolerability of a new drug. However, a proportion of the participants eligible for the study will have already taken the study drug. Those who are unable to tolerate it are therefore unlikely to take part in the extension study. The absence of this group of potential participants will introduce bias and increase the apparent tolerability of the new drug. Analysis strategies need to be developed and implemented to provide unbiased estimates of safety and tolerability.

All clinical research should have clear objectives and a clearly defined duration to which participants may consent. However, it is not uncommon to find protocols of open label extension studies that specify the duration of the study as "until licence approved." For some participants this could mean only a few weeks while for others it could be years, assuming the drug is ever licensed. Such studies seem to be designed only to promote the use of the study drug and serve no valid research purpose.

Dressing up marketing exercises as research lends them a spurious authority. It allows participants and clinicians to believe they are contributing something worthwhile to science rather than simply boosting market share for the relevant pharmaceutical company. As the guidelines of the Council for International Organisations of Medical Science state, "The ethical justification of biomedical research involving human subjects is the prospect of discovering new ways of benefiting people's health."[3] As marketing exercises clearly do not hold out any such prospect, they cannot count as ethical research activities. A key element of the ethical review of research is the appraisal of scientific merit, so the research ethics committee is placed in an invidious position by applicants seeking approval for such studies.

Summary points

- Open label extension studies are a common adjunct to double blind randomised controlled trials of new drugs
- The aim of open label extension studies often seems to be to enable continued use of a new drug for marketing or compassionate purposes rather than to increase knowledge
- The continued use of a new drug on compassionate grounds should not be considered within the research framework
- Patients should have full information available before deciding whether to participate
- Tighter criteria need to be applied to the ethical approval of extension studies

Compassionate use

When a promising new drug is being tested for a serious problem, doctors and patients naturally want the drug to be available outside the period of the randomised controlled trial. Delay is inevitable between the completion of the trial and the granting of a product licence, and participants who do well on the study drug will want to continue to take it. Research ethics committees often feel obliged to approve extension studies as the only practicable way to provide continued beneficial treatment. However, prescribing a drug on compassionate grounds is not research, and research ethics are therefore not a valid structure through which to provide a treatment, however beneficial. Members of research ethics committees will have had training and experience in assessing the ethical acceptability of a research protocol, but they will not necessarily have the expertise to make ethical judgments about clinical decisions involving the long term use of novel treatments. This may be the role of the institutional review board in some countries, but it is not the role of the UK research ethics committee system. Apart from their lack of relevant expertise, the research ethics committee is an independent body with no authority over clinical practice and no responsibility for decisions about practice.

At the end of a participant's involvement in a phase III study a decision will need to be made about their continuing treatment. The new drug may have been of appreciable benefit to the patient, and a mechanism is needed for the patient to receive the drug even if it is not yet licensed, especially if there are few other treatment options. However, this is not the role of an open label extension study, and research should not be used to mask the limitations of current regulations and procedures in drug development. Research ethics committees should not be expected to connive in such practices, no matter how laudable the intention.

Prescribing for compassionate use is possible on a named patient basis, and much has been published on the prescription of unlicensed and "off label" drugs. If researchers and clinicians believe there are grounds for

the compassionate use of an as yet unlicensed product, drug manufactures should be prepared to supply the drug to the doctors of patients who have been shown to benefit. The costs would, arguably, be no greater than those for an open label study. Safety data would still be available from these patients through the usual monitoring systems.

Future action

Some of our concerns may also apply to other trial designs, but our focus here is on the particular problems of open label extension studies. Several of the problems could be resolved by unblinding the allocation of participants as they complete the phase III study. Investigators object to this on the grounds that it may introduce bias, but participants could be informed of their status in the double blind trial by someone not involved in the analysis of the trial. It has been argued that unblinding should occur even if no open label study follows because the subsequent treatment of participants may be harmed if decisions are made about further management in ignorance of their response to the new drug.[4]

Open label extension studies are currently being misused for marketing purposes or to enable compassionate use of new drug. We recommend that recruitment and consent are dealt with more openly if the study follows a double blind trial and that potential participants are told which arm of the trial they were in before deciding whether to enrol. Research ethics committees should approve studies only if they address a genuine research question and have a clear rationale, end points, justification of sample size, time scale, and so on. If there is an argument for compassionate use, committees should advise use of mechanisms such as named patient prescriptions rather than open label extension studies.

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The rules

"Dear Editor, I read with interest your reworking of my manuscript. Firstly here are a few things that you did well: you checked the spelling thoroughly and you did improve the grammar. Here's what you could have done better: it would have been better if you hadn't completely changed the tone and style and meaning of my sentences. Yours etc."

Pendleton's rules are rules that help trainers give balanced feedback to trainees.[1] The idea is that, when giving feedback, learners and teachers should concentrate on the positive first and then say what they thought could have been done better. If you've done an advanced cardiac life support course in Britain then you'll be familiar with the rules. In the past many trainers were thought to be too destructive in their criticisms, and Pendleton's rules are an attempt to correct this.

But the rules do have their critics. Many say that they add an *Alice in Wonderland* air to training. I've had a few complaints as an editor and as a clinician, but none of them ever read like the above letter. So why do we encourage doctors to give and receive feedback in a way that they will never experience in real life? It can also be difficult to think of positive things to say to trainees who are still in the low foothills of the learning curve or who, worse still, have turned up to courses without having done any preparatory work. How do you then "accentuate the positive"? Do you say, "Well, at least you turned up"? Perhaps the most annoying thing about the rules is the insistence of some training providers that you must follow them—regardless of the learning style of the learners or the teaching style of the teacher.

Is there an alternative? Silverman et al have described a new way of giving feedback—called agenda-led, outcomes based analysis.[2] In this method you start with the learners' agenda and ask them what problems they experienced and what help they would like. Then you look at the outcomes that they are trying to achieve. Next you encourage them to solve the problems and then get the trainer and eventually the whole group involved. Feedback should be descriptive rather than judgmental and should also be balanced and objective.

If you are involved in teaching and learning then you may be interested in finding out more about these concepts. At BMJ Learning we are building up a resource of modules on learning and teaching. You can find out how to run a course, give a lecture, or even give feedback. You can give your views also. If you disagree with Pendleton's rules or with Silverman's ones or would even prefer a return to a 19th century "gloves off" approach to feedback then we are delighted to hear your views and to encourage debate.

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